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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,584	03/12/2001	Matthew L. Albert	600-1-276 CIP	5033

23565 7590 08/26/2004

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,584	ALBERT ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *5-14,20 and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,15-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action..

2. Claims 1-41 are pending. Claims 23-41, drawn to non-elected inventions are withdrawn from consideration. Claims 5-14 and 20, drawn to non-elected species are also withdrawn from consideration. Claims 1, 2 and 21 have been amended. Claims 1-4, 15-19, 21 and 22 are under consideration.

3. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 3 requires the absence of effective T-cell help by means pf excluding the CD+4 T-cells from the matured dendritic cells exposed to apoptotic cells. However, the claim requires the introduction of said dendritic cells into a mammal. It is unclear how CD+4 T-cell help can be excluded from interacting with the matured dendritic cells after infusion into said mammal without the aid of a drug which is administered in vivo. One of skill in the art would reasonably conclude that engagement of CD+4 T-cell help by CD+4 T-cells after infusion of the dendritic cells into said mammal would result in effective CD+4 T cell help. Without further guidance from the specification, one of skill in the art would not be able to carry out the invention of claim 3 in vivo without undue experimentation.

4. Claims 1, 2, 4, 15-17, 19, 21, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (Journal of Experimental Medicine, 1998, Vol. 188, pp. 1359-1368, cited in the previous Office action) in view of the abstract of Kirberg et al (European Journal of Immunology, 1003, Vol. 23, pp. 1963-1967) and Matzinger (Annual Review of Immunology, 1994, Vol. 12, pp. 991-1045) and Migita et al (Journal of Clinical Investigation, 1995, Vol. 96, pp. 727-732, cited in a previous Office action).

Claim 1 is drawn to a method for inducing tolerance in a mammal to an antigen comprising the steps of isolating peripheral blood mononuclear cells from said mammal; isolating dendritic cells from said peripheral blood mononuclear cells; exposing said dendritic cells ex vivo to apoptotic cells expressing said antigen in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4+T cell help, wherein said dendritic cells upon exposure to said dendritic cell maturation stimulatory molecule are characterized as having the phenotype CD14-, CD83+ and HLA-Drhi; and introducing a cellular portion of step (c) into said mammal; wherein said dendritic cells induce apoptosis of antigen-specific CD8+ T cells in said mammal resulting in tolerance to said antigen. Claim 2 embodies the method of claim 1 wherein dendritic cell maturation molecule is selected from the group consisting of PGE2, TNF-alpha,Il-6, Il-1 beta, LPS, monocyte conditioned medium, CpG-DNA or any combination thereof. Claim 4 embodies the method if claim 1 wherein said absence of effective CD4+ T-cell help is achieved by including in step (c) at least one agent that inhibits or eliminates effective CD4+ T cell help. Claim 15 embodies the method of claim 4 wherein said agent inhibits signaling consequent to dendritic-cell CD4 T cell engagement. Claim 16 embodies the method of claim 15 wherein said agent is a FKBP antagonist. Claim 17 specifies that the FKBP antagonist is FK506 (tacrolimus). Claim 19 embodies the method of claim 1 wherein said antigen is a viral antigen, a self antigen or a transplantation antigen. Claim 21 embodies the method of claim 1 wherein the infusion of the cellular portion of step (c) is done after the dendritic cells mature and exhibit the phenotype CD14-, CD83+ and HLA-Drhi. Claim 22 embodies the method of claim 1 wherein said mammal is human.

Albert et al teach that dendritic cells phagocytose apoptotic cells and cross present antigens from the apoptotic cells to cytotoxic T-lymphocytes (abstract). Albert et al teach that dendritic cells can acquire antigens from tumors, transplants, infected cells and self tissues for stimulation or tolerization of CTLs (abstract), thus fulfilling the specific limitation of claim 19 specifying the types of antigen for which tolerance might be evoked. Albert et al teach the isolation of dendritic cells from peripheral blood and the use of monocyte conditioned medium (MCM) as a maturation factor for the dendritic cells thus fulfilling the specific embodiments of claim 2 (page 1360, first column, lines 12-14 under the heading of "Preparation of Cells"). Albert et al also teach that on days 10 and 11, the cells were of the mature phenotype CD14-,

CD83+ and HLA-DRhi (page 1360, first column, lines 15-17 under the heading "Preparation of Cells"). Albert et al also teach the maturation factors of LPS, ceramide, CD40L, TNF-alpha and PGE2 in addition to macrophage conditioned medium (page 1359, second column, lines 13-17). Albert et al teach that the co-culture of immature dendritic cells with apoptotic cells in the presence of macrophage conditioned medium , a maturation stimulus for dendritic cells, made apoptotic cells and even better target for cross-presentation of antigen (page 1362, second column, lines 4-8).

The abstract of Kirberg et al teaches that CD+4 T-cell help prevents the rapid deletion of CD+8 T-cells after a transient response to antigen.

Matzinger teaches that CTL become unresponsive to their antigen if said CTL encounter said antigen first in the absence of CD4 help (page 1015, first full paragraph).

Migita et al teach that FK506 exclusively induced apoptosis of antigen-stimulated T-cells (page 731, first column, lines 11-16 of the first full paragraph, and second column, first paragraph).

It would have been prima facie obvious at the time the claimed invention was made to expose immature dendritic cells ex vivo to apoptotic cells in the presence of dendritic cell maturation factors of PGE2, TNF-alpha, Il-6, Il-1-beta, LPS or monocyte conditioned medium and introduce said matured dendritic cells into a mammal in the presence of FK506. One of skill in the art would be motivated to do by the teachings of Albert et al on the maturation of dendritic cells exposed to apoptotic cells in the presence of the maturation factor, MCM, and the suggestion of Albert et al that the presence of CD+4 T-cell help is necessary for the full activation of T-cells and the teachings of Kirberg et al on the rapid deletion of CD+8 T cells after transient response to antigen when the T-cell encounters said antigen in the absence of CD+4 T cell help. One of skill in the art would under stand that the administration of the matured dendritic cells exposed to apoptotic cells and the maturation stimulatory factors would be potent antigen-presenting cells and cause activation of CD+8 T-cells specific for the antigens derived from the apoptotic cells. One of skill in the art would understand by the teachings of Kirberg et al that the specific CD+8 T-cells would be eliminated apoptotically after this transient activation in the absence of effective CD+4 T-cell help. One of skill in the art would recognize that FK506

would induce apoptosis of antigen-stimulated T-cells which include CD+4 T-cells and would be effective at eliminating CD+4 T-cell help.

5. Claims 1, 2, 4, 15-19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (Journal of Experimental Medicine,) in view of the abstract of Kirberg et al (European Journal of Immunology, 1003, Vol. 23, pp. 1963-1967) and Matzinger (Annual Review of Immunology, 1994, Vol. 12, pp. 991-1045) and Migita et al (Journal of Clinical Investigation, 1995, Vol. 96, pp. 727-732, cited in a previous Office action) as applied to claims 1, 2, 4, 15-17, 19, 21 and 22 above, and further in view of Li et al (Transplantation, 1998, Vol. 66, pp. 1387-1388, cited in a previous Office action) and Sehgal (Clinical biochemistry, 1998, Vol. 31, pp. 335-340, cited in a previous Office action).

Claim 18 embodies the method of claim 16 wherein said TOR antagonist is rapamycin. The combination of Albert et al and Matzinger and the abstract of Kirberg et al and Migita et al render obvious claims 1, 2, 4, 15-17, 19, 21 and 22 with respect to the administration of FK506 as an agent which eliminates effective CD+4 T-cell help by means of inhibiting dendritic-cell Cd+4 T-cell signaling consequent to dendritic cell CD+4 T-cell engagement. None of the references teach rapamycin as an agent which eliminates dendritic-cell Cd+4 T-cell signaling consequent to dendritic cell CD+4 T-cell engagement.

Li et al teach that CTLA4Ig combined with rapamycin results in a permanent tolerization to a tissue engraftment. Li et al teach that rapamycin blocks Il-2 induced proliferative but not apoptotic signals required to achieve tolerance to an antigen (page 1387, second column, second full paragraph). Sehgal teaches that rapamycin complexes with the immunophilin FKBP to produce the mammalian inhibitor of rapamycin complex which blocks the Il-2 mediated signal transduction pathway that prevents cell cycle progression from G1 to S-phase in T-cells (page 336, second column, lines 4-9).

It would have been prima facie obvious at the time the claimed invention was made to substitute rapamycin for FK506 in the method rendered obvious by the combination of Albert et al and Kirberg et al and Migita et al. One of skill in the art would have been motivated to do so by the teachings of Li et al on the blockage of Il-2-idnuced proliferative signals by rapamycin and the teachings of Sehgal et al that rapamycin blocks the Il-2 signal transduction pathway that

prevents T-cells from entering the S-phase and thus proliferating. One of skill in the art would recognize from the teachings of Sehgal et al that rapamycin would prevent the proliferation of activated T-cells which include CD+4 T cells; one of skill in the art would recognize from the teachings of Li et al that rapamycin would not inhibit an Il-2 induce apoptotic signal and thus not block the apoptosis of antigen-stimulated CD+4 T-cells or CD+8 T cells.

6. In response to applicant's argument that the references as a whole do not render obvious the instant invention, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

7. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

8. All other rejections and objections as set forth in the previous Office action are withdrawn.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/23/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER